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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/611,398

06/30/2003

Mariagrazia Pizza

PP00338.105

1890

27476

7590

11/20/2008

NOVARTIS VACCINES AND DIAGNOSTICS INC.

INTELLECTUAL PROPERTY R338

P.O. BOX 8097

Emeryville, CA 94662-8097

EXAMINER

GRASER, JENNIFER E

ART UNIT

PAPER NUMBER

1645

MAIL DATE

DELIVERY MODE

11/20/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/611,398

Applicant(s)

PIZZA ET AL.

Examiner

Jennifer E. Graser

Art Unit

1645

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on RCe 10/27/08.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 10-19 and 23-25 is/are pending in the application.
- 4a) Of the above claim(s) 10-18 and 24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 19, 23 and 25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/27/08 has been entered.

Claims 1-4, 19, 23 and 25 are currently under examination. Claims 10-18 and 24 were previously withdrawn from consideration as being drawn to a non-elected invention.

Rejections Withdrawn:

2. The former under 35 U.S.C. 102(b) as being anticipated by Dominighini et al (WO 93/13202) in light of evidence provided by Pizza (1994) has been overcome in light of the claim amendments and arguments.

The former 112, first paragraph enablement rejection has also been overcome in light of the claim amendments and arguments.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1-4, 19, 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domenighini et al (WO 93/13202) in view of Pizza (1994) and Clements et al (US Pat.6,019,982).

Domenighini et al disclose an immunogenic detoxified protein comprising the amino acid sequence of the subunit A of an Escherichia coli heat labile toxin (LT-A, see claims 1-3) the protein having possible mutations at positions Ser-63 **and** Arg-192 and vaccine compositions comprising said protein. Domenighini specifically recites that position Ser-63 of CT-A or LT-A may be replaced with another amino acid (and more specifically Ser-63-Lys in claim 3) and claim 2 specifically recites at least one additional amino acid specifically (including Arg-192) may also be replaced with another amino acid, i.e., Domenighini teaches double mutants. Domenighini also teaches the substitution of Arg-192-Asn in Table 1; however this single mutation alone did not appear to reduce toxicity. The use of pharmaceutically acceptable carriers and adjuvants are recited on page 14 and the paragraph bridging pages 8-9. The use of the B subunit is taught on page 8, lines 11-30. The use of an additional immunogenic antigen is taught throughout as well as at page 23.

Pizza (1994) teach Lys63 causes loss of toxicity (see (Table 1 and 2) and Arg-192-Asn decreases the rate of proteolysis and activation in vivo (see entire reference). The reference teaches DNA molecules that encode mutant detoxified heat labile toxin of E.coli and mutant detoxified cholera toxin, wherein the mutations are in A-subunit in positions 63 and 192, but does not show the codon mutation at position 192 to be a mutation from Arg-192 to Gly- 192. Clements et al show DNA that encodes a

mutant detoxified heat labile toxin of E.coli and mutant detoxified cholera toxin, wherein the mutation at position 192 is mutation from Arg-192 to Gly-192 in an analogous art for the purpose of obtaining a detoxified protein that still evidences adjuvant activity for induction of an enhanced immune response.

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to modify the mutation of Domenighini at position 192 from Asn to Gly as taught by Clements or Pizza, in addition to the Ser-63-Lys mutation taught by Domenighini, because Clements and Domenighini et al are both directed to the site directed mutagenesis of heat labile toxin of E.coli at position Ser-63 and Arg-192, and Clements et al teaches the advantage of substituting Gly at position 192 as yielding a stable, detoxified, mutant that is devoid of ADP-ribosyl transferase activity, but retains its activity as an immunological adjuvant (see Clements, col. 8, lines 24-27 and 28-50). The person of ordinary skill in the art would have been motivated to substitute the amino acid for Gly at position 192, because the resultant protein/polypeptide would lack the potential to become toxic due to proteolytic activation, resulting in "no real or potential side-effects, such as diarrhea, associated with its use (see col. 10, lines 5-14). In the absence of a showing of unexpected results, Domenighini et al in view of Pizza and Clements et al obviate the instantly claimed invention. Domenighini specifically teaches additional mutations to the mutant with a mutation at Ser-63-Lys and the Pizza and Clements teach that Arg-192 substituted with either Asn or Gly decreases the rate of proteolysis and activation in vivo (see entire reference). This detoxified protein would inherently have a toxicity less than 0.01% of

the naturally occurring toxin counterpart, particularly because it is identical to that of the protein instantly claimed and Domenighini et al show in Table 1 on page 46 that a Ser-63-Lys mutation renders a non-toxic polypeptide even when it is undiluted. The use of an additional immunogenic antigen is taught throughout as well as at page 23 and it would have been prima facie obvious that an additional antigen could be used to provide a multivalent immune response as was well known in the prior art.

Applicants' arguments are rendered moot in light of the new rejection.

5. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645

11/19/08